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Short reports

Fortuitous detection of uniparental isodisomy of chromosome 6

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Abstract
Uniparental isodisomy is defined as the inheritance of two copies of the same parental chromosome and can result in defects when it produces homozygosity for a recessive mutation or in the presence of imprinting. We describe the detection of a chromosome 6 uniparental isodisomy in a 9 year old girl, discovered during a search for an HLA identical sib. HLA typing, erythrocyte phenotyping, and genotypes of microsatellite polymorphisms were compatible with a paternal isodisomy of chromosome 6, with normal biparental origin of the other chromosomes. Paternal cells were not responsive to the patient's cells in mixed lymphocyte cultures. This fortuitous detection of a chromosome 6 isodisomy suggests that cases of chromosome 6 UPD may not be deleterious and may therefore go undetected.
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In 1980, Engel[1] defined theoretically the concept of uniparental disomy (UPD) as the inheritance of both copies of a chromosome from only one parent. The majority of UPD cases result from meiotic non-disjunction events.[2] Two subtypes of UPD can be established: heterodisomy occurs when the inheritance of genetic material is from both chromosomes of a parental pair; isodisomy is present when two copies of the same parental chromosome are inherited, a condition with increased risk for recessive disorders. However, heterodisomy and isodisomy are not mutually exclusive for a given chromosome, and therefore UPD may have both heterodisomic and isodisomic segments. Both forms of UPD can cause disorders by unmasking genomic imprinting. Several reported cases of UPD involving various chromosomes are associated with deleterious effects.[2,3] We describe here a fortuitously discovered case of chromosome 6 paternal isodisomy.

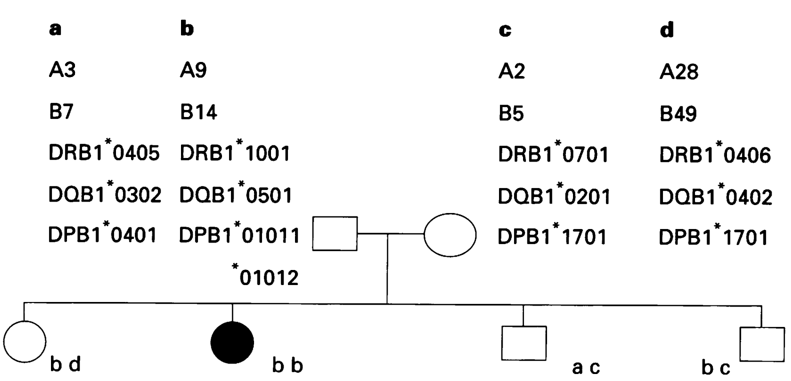

Figure 1 HLA typing of the family. The patient is represented by a solid symbol. The haplotypes were deduced by segregation analysis and are indicated by arbitrary lower case letters.

The patient is a 9 year old girl, of Algerian origin, with β thalassaemia major confirmed by haemoglobin electrophoresis. No phenotypic abnormalities were noted on physical examination other than mild growth retardation probably related to her red blood cell disorder. Her weight and height at birth were 2800 g (25th centile) and 50 cm (75th centile) and at present are 20 kg (10th centile) and 123 cm (25th centile). She and her family were referred for HLA typing to identify potential donors for allogeneic bone marrow transplantation (BMT). HLA class I typing of all family members was performed using the standard microlymphocytotoxicity test. HLA class II typing was performed by hybridisation with sequence specific oligonucleotides after polymerase chain reaction DNA amplification for DRB1, DQB1, and DPB1 loci.

HLA typing of the family and segregation analysis showed that the patient was homozygous for the paternal haplotype with no inheritance of a maternal haplotype (fig 1). The other sibs had normal inheritance of both maternal and paternal HLA haplotypes. Karyotype analysis of the patient was normal. Phenotyping of erythrocyte markers (for which the genes are located on chromosomes 1, 4, 7, 18, 19, and 22) was performed. Additional genotypes were obtained for the patient and her parents at five highly informative microsatellite polymorphisms from chromosome 6 (6p and 6q) as well as from seven other autosomes (table 1). The results were entirely compatible with a paternal isodisomy of chromosome 6 with normal biparental origin of the other chro-

Table 1 Microsatellite polymorphism genotyping of chromosome 6 and seven other autosomes

	Chromosome 6					chr 1	chr 5	chr 7	chr 11	chr 12	chr 15	chr 19
	SCA1 (6p)	HLA superlocus (6p)	TNFα (6p)	TNFβ (6p)	D6S1009 (6q)	D1S436	D5S351	D7S507	D11S1985	D12S79	GABRA	APOC2
Father	1 2	1 2	1 3	2 3	1 2	1 4	3 4	2 3	1 2	1 2	1 3	1 2
Child	2 2	2 2	3 3	3 3	1 1	1 3	2 4	1 2	1 3	2 3	2 3	1 3
Mother	3 3	3 4	1 2	1 2	3 3	2 3	1 2	1 1	3 4	2 3	2 2	3 4

Table 2 Mixed lymphocyte culture results

Responder cells	Stimulator cells* (cpm) SRR%†			
	Proband	Mother	Father	Control‡
Proband	2550	19527 56%	15126 46%	36969
Mother	19803 87%	1112	46283 109%	53379
Father	1085 0.8%	37675 99%	942	66379
Control‡	24754	49283	45124	57550
100% RR	41	88	79	—

* Stimulator cells were irradiated with 3000 rads.
† Stabilised relative response (RR): [RR of responder to control/100%RR (RR of control to HLA mismatched control stimulator)] × 100.
‡ Mean values. Three different unrelated HLA mismatched donors were used as controls.

mosomes (probability of maternity >99.9%, Bayes theorem). However, because only one 6q marker was used, we cannot formally exclude the possibility of combined heterodisomy and isodisomy in this case. The β thalassaemia trait was found in both parents. Microsatellite analysis excluded the possibility of uniparental isodisomy also at chromosome 11, which contains the β globin locus.[4] Measurement of serum C4 levels showed normal results for the patient.

As expected with a paternal isodisomy of chromosome 6, mixed leucocyte cultures showed that the patient's cells did not stimulate paternal responder cells and that the patient's cells were, however, capable of responding to the father's cells (table 2). The reduced responsiveness of the proband's cells to her mother's cells could be explained by the hypothetical influence of NIMAs (non-inherited maternal HLA antigens), as previously postulated.[5]

In summary, we present the occurrence of a paternal isodisomy of chromosome 6 in a 9 year old girl with no apparent abnormality other than those related to β thalassaemia. Uniparental disomy is a rare but recognised cause of at least three genetic disorders in humans and has been documented in several other pathological conditions involving different chromosomes.[2,3] Reported cases of paternal isodisomy of chromosome 6 were associated with deficiency of the fourth component of complement[6] and neonatal diabetes mellitus.[7,8] In this respect, it has been suggested that an imprinted gene on chromosome 6 is central to the development and maturation of early fetal and neonatal pancreatic β cell function.[8] In our patient, no evidence for transient neonatal diabetes was found at birth. However, we cannot formally exclude this possibility. Maternal isodisomy of chromosome 6 in a renal transplant patient with no other genetic abnormality was recently reported.[9]

Uniparental disomy may hypothetically result in a pathology when it produces homozygosity for a recessive mutation or for imprinted genes.[2,3] The description of both maternal and paternal isodisomy of chromosome 6, with no apparent phenotypic abnormalities, suggests that there is no imprinting of genes on maternally and paternally derived chromosomes 6. The fortuitous detection of chromosome 6 UPD in a β thalassaemia patient indicates that some cases of UPD may go undetected in the population. However, the fact that this is the first such fortuitous detection of paternal UPD for an intensively studied chromosome (because of HLA typing) confirms the rarity of this condition. The results of HLA typing and mixed lymphocyte cultures suggest that the risk of graft *v* host reaction associated with the use of the father for BMT would be acceptable.

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